

REVIEW ARTICLE

Complications of COVID-19 Vaccines during Pregnancy; a Systematic Review

SeyedAhmad SeyedAlinaghi¹, Mehrzad MohsseniPour¹, Solmaz Saeidi², Pedram Habibi¹, Mohsen Dashti³, Newsha Nazarian⁴, Tayebeh Noori⁵, Zahra Pashaei¹, AmirBehzad Bagheri⁶, Afsaneh Ghasemzadeh³, Amir Masoud Afsahi⁷, Narjes Aghaie⁸, Paniz Mojdeganlou⁹, Ghazal Arjmand⁹, Ghazal Zargari¹⁰, Roshanak Modiri¹, Hengameh Mojdeganlou¹¹, Armin Razi¹², Esmail Mehraeen^{13*}, Omid Dadras^{1,14}

1. Iranian Research Center for HIV/AIDS, Iranian Institute for Reduction of High Risk Behaviors, Tehran University of Medical Sciences, Tehran, Iran.
2. Department of Nursing, Khalkhal University of Medical Sciences; Khalkhal, Iran.
3. Department of Radiology, Tabriz University of Medical Sciences, Tabriz, Iran.
4. School of Medicine, Islamic Azad University, Tehran, Iran.
5. Department of Health Information Technology, Zabol University of Medical Sciences, Zabol, Iran.
6. Student Research Committee, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran.
7. Department of Radiology, School of Medicine, University of California, San Diego (UCSD), California, USA.
8. School of Nursing and Midwifery, Tehran University of Medical Sciences, Tehran, Iran.
9. Shahid Beheshti University of Medical Sciences, Tehran, Iran.
10. School of Medicine, Iran University of Medical Sciences, Tehran, Iran.
11. Department of Pathology, Urmia University of Medical Sciences, Urmia, Iran.
12. School of Medicine, Tehran University of Medical Sciences, Tehran, Iran.
13. School of Medicine, Tehran University of Medical Sciences, Tehran, Iran.
14. Department of Global Public Health and Primary Care, Graduate School of Medicine, University of Bergen, Bergen, Norway.

Received: July 2022; Accepted: August 2022; Published online: 24 September 2022

Abstract: **Introduction:** Rare serious complications have been documented after COVID-19 vaccination as clinical research proceeded and new target populations, such as children and pregnant women, were included. In this study, we attempted to review the literature relevant to pregnancy complications and maternal outcomes of COVID-19 immunization in pregnant women. **Methods:** We searched the databases of PubMed, Scopus, Cochrane, and Web of Science on 31 August 2022. The records were downloaded and underwent a two-step screening; 1) title/abstract and then 2) full-text screening to identify the eligible studies. We included English original studies that evaluated the adverse effects of COVID-19 vaccines during pregnancy. Information such as the type of study, geographical location, type of vaccine injected, gestational age, maternal underlying diseases, and complications following the vaccination were extracted into pre-designed tables. **Results:** According to the findings of included studies, in most of them vaccination had a positive impact and no negative effects were observed. Also, no medical history was reported in 11 articles, and pregnant women had no underlying diseases. Some serious adverse events were reported after vaccination, including miscarriage, paresthesia, uterine contraction, vaginal bleeding, preterm birth, major congenital anomalies, intrauterine growth restriction, and seizure. **Conclusion:** Because of limited data availability and the cross-sectional design of most studies, we could neither infer causation between vaccines and incidence of adverse effects nor comment with certainty about any possible adverse outcome of COVID-19 vaccines in vaccinated pregnant women. Consequently, more longitudinal and experimental studies are needed to define the exact adverse effects of COVID-19 vaccines in pregnant women.

Keywords: Drug-related side effects and adverse reactions; COVID-19; COVID-19 vaccines; pregnancy; SARS-CoV-2

Cite this article as: SeyedAlinaghi SA, MohsseniPour M, Saeidi S, Habibi P, Dashti M, et al. Complications of COVID-19 Vaccines during Pregnancy; a Systematic Review. Arch Acad Emerg Med. 2022; 10(1): e76. <https://doi.org/10.22037/aaem.v10i1.1622>.

*Corresponding Author: Esmail Mehraeen, Department of Health Infor-

mation Technology, Khalkhal University of Medical Sciences, Khalkhal, Iran.



1. Introduction

Putting an end to the pandemic has been the ultimate goal of humanity since the commencement of the COVID-19 pandemic and substantial efforts have been made to develop an effective vaccine to curb the virus ever since. As a result of advancements in COVID-19 prevention research, many countries have developed coronavirus vaccines (1-3). The development of these vaccines, each of which inhibit Coronavirus infection using a different mechanism, raises the hopes of ending the COVID-19 pandemic. Although COVID-19 vaccination lowers the chance of acquiring the coronavirus and its mortality with no or minimal major side effects (4, 5), rare serious complications have been documented after COVID-19 vaccination as clinical research proceeded and new target populations, such as children and pregnant women, were included (6).

Serious side effects of vaccines have been reported in the past, and such side effects have not been specific to COVID-19 vaccines. For instance, the Influenza vaccine may have some serious side effects such as Guillain-Barré syndrome and acute transverse myelitis (7-9). Likewise, COVID-19 immunization may potentially cause acute transverse myelitis in rare cases (10).

It has been shown that pregnant women could be at a higher risk of severe COVID-19 infection (11) and COVID-19 infection in a pregnant mother is more likely to harm her or her fetus. It appeared that caesarean sections and premature deliveries may be more likely in severe COVID-19 among pregnant patients (12). These findings emphasize the important role of COVID-19 immunization in pregnant women. Therefore, it is of paramount importance to explore the possible side effects of COVID-19 vaccination in pregnant women using available data. Since pregnant women were not included in initial vaccine trials, limited information exists on the vaccine's efficacy and safety during pregnancy. Although several studies reported different side effects of COVID-19 vaccines in the general population, there is a scarcity of literature on pregnant women (3, 13, 14). Therefore, more research concerning the effectiveness and possible side effects of COVID-19 vaccination in pregnant women is needed. Due to the novelty of COVID-19 vaccination, we attempted to review the literature relevant to pregnancy complications and maternal outcomes of COVID-19 immunizations in this systematic review.

Postal Code: 5681761351, Tel: +98-45-32426801, Fax: +98-45-32422305, E-mail: es.mehraeen@gmail.com.

2. Methods

2.1. Search strategy

This systematic review was reported in adherence to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) checklist. We searched the databases of PubMed, Cochrane, Scopus, and Web of Science on 31 August 2022. To develop our search strategy, we checked the keywords from previous studies and the medical subject headings (MeSH) website. The search strategies for each database are reported below as an example:

((COVID-19 [Title] OR SARS-CoV-2 [Title] OR Novel coronavirus [Title] OR 2019-nCoV [Title]) AND (vaccine [Title] OR vaccination [Title] OR vaccinated [Title] OR immunization [Title])) AND (side effect [Title] OR adverse effect [Title] OR adverse reaction [Title] OR adverse event [Title] OR safety [Title])) AND (pregnancy [Title] OR pregnant [Title] OR gestation [Title] OR gestational [Title])

PICO

1. Population: Pregnant women
2. Intervention: Receiving COVID-19 vaccines
3. Comparison: Not receiving COVID-19 vaccines
4. Outcomes: Various adverse events

Inclusion/exclusion criteria

We included English original studies that evaluated the adverse effects of COVID-19 vaccines during pregnancy. We did not impose any restrictions regarding the date of the studies or the length of their follow-up in this systematic review.

The exclusion criteria were the following:

- 1) Non-original studies (reviews, opinions, etc.)
- 2) Non-English studies
- 3) Studies not related to the aim of this systematic review (e.g. not related to COVID-19 vaccines, not related to pregnancy, did not measure adverse effects, etc.)
- 4) Studies not conducted in humans
- 5) Abstracts or studies that lacked available full-texts

2.2. Study selection process

Two independent researchers screened the studies in a two-step method. First, they screened the studies based on the contents of their title and abstracts. Then, the eligible studies entered the second step, which was the full-text screening. Studies that adhered to the inclusion criteria in both steps were finally included in this systematic review. In case of any disagreements between the researchers, they asked the opinion of another researcher to resolve the matter.

2.3. Data extraction

Three independent researchers extracted the data of the included studies into a pre-designed word table (one third of the studies were given to each researcher). The following information were extracted: type of the study, country, study



population, vaccine type, gestational age (week/trimester), past medical history, and reported complications (typical side effects or serious adverse events). Another researcher checked the extracted data and corrected any possible mistakes. The extracted data were qualitatively synthesized, but we did not aim to perform statistical analysis as the study is not a meta-analysis.

2.4. Risk of bias/quality assessment

We assessed the risk of bias/quality of the studies using the Newcastle-Ottawa scale (NOS) checklist. This scale allocates a 0-9 score to each study based on selection, comparability, and exposure/outcome (15). Studies that scored 4 or below were considered of poor quality.

3. Results

A total of 1447 relevant studies were identified applying different combinations of keywords and search strategies in online databases. Following the initial review, 408 duplicates were deleted. The remaining articles (n=1039) were screened by two independent researchers based on their title and abstract. In the next step, the full-text of 470 remaining articles were thoroughly read and based on eligibility criteria, the most relevant records were selected for final qualitative synthesis. During data extraction, 450 articles were removed because they were non-English articles (n=25), papers with the lack of experimental data (n=392), and animal or pure lab-based studies (n=33). Finally, 20 studies met the inclusion criteria and were included (Figure 1).

Variables including type of vaccine, sample population, age, complications, gestational age, and prior medical history were extracted and are reported in Table 1. Included articles investigated the side effects and adverse events of COVID-19 vaccines including Pfizer-BioNTech, Moderna, and Janssen. The study designs included case report, case series, and cross-sectional and cohort studies.

According to the findings of included studies, in most cases vaccination had a positive impact and no negative effects were observed. There were no notable differences between the vaccinated and unvaccinated groups in 11 studies. In two studies, complications were reported more in the vaccinated group than in the unvaccinated group. In a study conducted among 390 pregnant women, paresthesia was significantly more common among vaccinated pregnant women compared to unvaccinated group. Also, in those who received the 2nd dose in the third-trimester, uterine contractions were significantly more common (16). Two newborn babies of 84 pregnant women who had received Pfizer (49%), and Moderna (51%) vaccines, were admitted to the intensive care unit to receive respiratory support. One baby received continuous positive airway pressure (CPAP) and one of them

had transient tachypnea of the newborn (17).

No medical history was reported in 11 articles, and pregnant women had no underlying diseases. However, in a cohort study conducted on 7350 pregnant women, underlying disease of diabetes mellitus, hypertension, Immunosuppression/cancer, obesity (BMI \geq 30), infertility, chronic kidney disease, cardiovascular disease, and chronic obstructive pulmonary disease were reported (18, 19). In another cohort study in 84 pregnant women who were in their first (13.1%), second (46.4%), and third (40.5%) trimesters of pregnancy, diabetes mellitus, hypertension, obesity (BMI \geq 30), asthma, Immunosuppression/cancer, and previous SARS-CoV-2 infection were reported as underlying diseases (17). Chronic liver disease, chronic heart disease, diabetes mellitus, and hypertension in 390 pregnant women in all three trimesters of pregnancy were reported (16). The time between vaccine inoculation and the onset of adverse events of idiopathic thrombocytopenic purpura (ITP) symptoms was 11 days in a woman who was in her first trimester of pregnancy (20) and it was 12 days in 30 pregnant women who were in their first (17%), second (50%), and third (33%) trimesters of pregnancy (21).

In a matched cohort of 133 vaccinated and 399 unvaccinated pregnant women who had received Pfizer and Moderna, the rates of adverse pregnancy outcomes were similar between vaccinated and unvaccinated pregnant women: postpartum hemorrhage (9.8% vs 9%), fetus small for gestational age (12% vs 12.8%), maternal high-dependency unit or intensive care admission (6% vs 4%), neonatal intensive care unit admission (5.3% vs 5%), fetal abnormalities (2.2% vs 2.5%), and stillbirth (0% vs 0.2%). In the vaccinated group, three fetal abnormalities including spina bifida, ventriculomegaly, and hydronephrosis were reported. The spina bifida case was diagnosed before the first dose of the COVID vaccine. The ventriculomegaly case was diagnosed at 37 weeks gestation with no associated brain abnormalities. The hydronephrosis appeared to be mild with no associated abnormality at birth (22). In another cohort study conducted on 827 pregnant women who received Moderna (46%) and Pfizer (54%) vaccines, 46 cases of spontaneous abortion, and three cases of stillbirth, premature rupture of membrane, and vaginal bleeding, each, were reported. No congenital anomalies were observed (23).

In a case report, a pregnant woman who received Moderna in the first trimester manifested ITP symptoms including acute bruising and petechiae, she was discharged after three days of hospitalization and completely recovered following a course of steroid treatment (20). In a case-control study, 390 pregnant women who received Pfizer in their first (19.5%), second (49.5%), and third (31%) trimesters, experienced the following adverse events: axillary lymphadenopathy (0.3%), paresthesia (2.3%), uterine contraction (1.3%), and vagi-



Table 1: Complications of COVID-19 vaccination during pregnancy

ID	The first author (r)	Type of study	Sample size	Type of Vaccine	Gestational Age (%)	Medical history (%)	Complication (%)		Other findings
							Adverse events	Side effects	
1	Blakeway, H. (22) UK	Cohort	1328	PB, M	N/A	N/A	Spina bifida, ventriculomegaly, hydronephrosis, fetal abnormalities, postpartum hemorrhage	N/A	N/A
2	Carrie Bennett (20) USA	Case report	1	M	First trimester	N/A	ITP symptoms: acute bruising and petechiae	N/A	Discharged after 3 days of hospitalization, to continue steroids for one week and taper over 6 weeks.
3	S. BooksteinPeretz (16) Israel	Case-control	390	PB	First trimester (19.5), second trimester (49.5), third trimester (31)	Diabetes mellitus (3.3), chronic heart disease (0.8), chronic liver disease (5.4), hypertension (0.5)	Axillary lymphadenopathy (0.3), paresthesia (2.3), uterine contraction (1.3), vaginal bleeding (0.3), two babies admitted to ICU	Local pain (91.8), rash (0.8), fever (1.5), severe fatigue (25.6), arthralgia (1), myalgia (5.9), headache (4.6)	Paresthesia among pregnant women was significantly more common. In those who received 1st dose during the third trimester, local pain/swelling was significantly less common and in those who received 2nd in third-trimester uterine contractions were significantly more common.
4	Tom T. Shimabukuro (23) USA	Cohort	827	PB (54) M (46)	N/A	N/A	Pregnancy losses (13.9), preterm birth (9.4), small for gestational age (3.2), major congenital anomalies (2.2)	N/A	live-born infants=724 multiple gestation=12
5	Megan E Trostle (24) USA	Cross-sectional	424	mRNA	First trimester (34), second trimester (54.4), third trimester (11)	N/A	Spontaneous abortions (2.12), Terminated pregnancies (0.7), Intrauterine growth restriction (0.6), anomalies (1.5), preterm birth (5.9), need for NICU (15.3), small for gestational age (12.2)	N/A	N/A
6	Regan N. Theiler (28) USA	Cohort	2002	mRNA	Median gestational age 32 weeks	N/A	No adverse events were reported.	N/A	N/A
7	Tamar Wainstock (29) Israel	Cohort	913	PB	3rd trimester	N/A	No adverse events were reported.	N/A	N/A
8	Lauren Head Zauche (27), USA	Cohort	2456	mRNA	Prior to 20 weeks' gestation	N/A	N/A	N/A	N/A

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ID	The first author (r)	Type of study	Sample size	Type of Vaccine	Gestational Age (%)	Medical history (%)	Complication (%)		Other findings
							Adverse events	Side effects	
9	Renuka Ananth (25) USA	cross-sectional	38	PB (52.6) M (47.4)	N/A	N/A	Seizure (2.6)	Sore arm or pain (97.3), fatigue (57.8), headache (50), chills (47.3), myalgia (34.2), nausea (28.9), fever (15.7), sweating (15.7), feelings of joy (10.5), rash (10.5), joint pains (7.8), swelling (7.8), flushing (7.8), reduced mental clarity (7.8), itching (5.2), decreased appetite (5.2), decreased sleep quality (5.2), Palpitations or increased heart rate (5.2), heat or cold intolerance (5.2), anxiety (5.2), heartburn (5.2), muscle spasm (2.6), nasal congestion (2.6), increase in sleep (2.6), vomiting (2.6)	N/A
10	Kathryn J. Gray (17) USA	Cohort	84	PB (49) M (51)	Trimester of first vaccine dose: first (13.1), second (46.4), third (40.5)	Chronic hypertension (4), diabetes mellitus or gestational diabetes (4%), BMI of >30 (12%), asthma (19), immunosuppression/cancer (4), previous SARS-CoV-2 infection (2)	N/A	Injection site soreness (67.8), injection site reaction or rash (1.2), headache (9.5), muscle aches (2.4), fatigue (16.6), fever or chills (1.2), elevated heart rate, joint pain, nausea, swollen lymph node, and sore throat, joint pain, nausea, sore throat, dizziness, stomach ache, night sweats, clogged ears	Two newborn babies were admitted to the intensive care unit to receive respiratory support. One baby received CPAP and one of them had TTN.
11	Collier A-RY (21) Israel	Cohort	30	PB (36.6) M (63.3)	1st trimester (17), 2nd trimester (50), and 3rd (33)	N/A	N/A	Fever (13.3)	N/A
12	Goldshtein I (18) Israel	Cohort	7530	PB	N/A	Obesity (BMI ≥30), infertility, cancer, hypertension, chronic kidney disease, diabetes, prediabetes, cardiovascular disease, chronic obstructive pulmonary disease	SARS-CoV-2 hospitalization (0.2), abortion (1.7), intrauterine growth restriction (0.5), stillbirth (<0.1), preeclampsia (0.3), preterm birth (<37 weeks) (5.6)	Headache (0.1), general weakness (0.1), stomachache (<0.1), non-specified pain (<0.1), dizziness (<0.1), rash (<0.1), eye burning or blurred vision (<0.1)	There were no notable differences between the vaccinated and unvaccinated groups.



Table 1: Complications of COVID-19 vaccination during pregnancy

ID	The first author (r)	Type of study	Sample size	Type of Vaccine	Gestational Age (%)	Medical history (%)	Complication (%)		Other findings
							Adverse events	Side effects	
13	Kachikis A (39) USA	Cohort	7809	PB (61.2) M (38) J (0.8)	1st trimester (23.3), 2nd trimester (47.3), 3rd trimester (26.8)	N/A	Miscarriages (0.7),	Pain at the injection site, fatigue, myalgia, headache, chills, fever	N/A
14	Abraham B (35) Qatar	case report	1 (female)	PB	25 ± 2 weeks	Hypothyroidism, mild COVID-19 infection	Acute respiratory distress syndrome with the following signs and symptoms: hypotension, decreased O2 saturation, bilateral bronchial breath sounds, right lower lobe consolidation with extensive diffuse infiltrates in CXR, dilated pulmonary trunk and right lower lobe consolidation with an associated bilateral diffuse area of ground glass consolidation in CT scan, myocarditis, mild rise in troponin-I, tachypnea, increased white blood cell count (22.09 × 10 ⁹), increased C-reactive protein (356 mg/L), need to a short period of mechanical ventilation and steroid therapy	Fever, pleuritic chest pain, shortness of breath on exertion, sweating, palpitation,	A healthy term male baby was born
15	Ben-Mayor Bashi T (37) Israel	cohort	58: (32.7% receive only a single dose, 67.3% receive two doses)	PB	First dose: 34.5 weeks Second dose: 37.0 weeks	BMI ≥ 30 (3.6),	Admission to NICU (1.7)	At first/second dose of vaccine: pain at injection site (24.1)/ (20.5) back pain (3.4)/0 fatigue/weakness (15.5)/ (23.0) chills (5.1)/ (12.8) myalgia (5.1)/ (12.8) fever 0/ (2.5) headache (8.6)/ (5.1) peripheral facial nerve paralysis (1.7)/0 nausea (1.7)/0 dizziness (1.7)/ (2.5) unspecified illness (5.1)/ (10.2), enhanced fetal movements perception (1.7)/0	13 days after administration of the first dose of the covid-19 vaccine the levels of covid-19 IgG antibody in maternal sera of vaccinated women were positively correlated with same antibody level in cord blood sera
16	Arulappen AL (36) China	cohort	121	mRNA	First trimester (4.9%), Second trimester (71.9%), third trimester (23.1%)	Gestational diabetes mellitus (14.5%), anemia (8.1%), hyperthyroidism (1.6%), asthma (0.8%), impending eclampsia (0.8%),	Miscarriages (0.82%), small for gestational age (5.8%), anomalies (bilateral clubfoot, glucose-6phosphate dehydrogenase (G6PD) deficiency and sacral dimple): (2.5%) jaundice (85.8%), serious complaints during the first month of life (constipation, need for oxygen therapy because of Respiratory Distress Syndrome) (1.7%), preterm birth (≤37 weeks) (11.7%), admission to NICU (22.5%), neonatal infection (11.7%)	Pain, body ache, headache, chills, shivering, and fatigue	No neonatal death was reported

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							Adverse events	Side effects	
17	Blakeway H (38) UK	Cohort	1328V (vaccinated: 140, unvaccinated: 1188)	PB (90.7%), viral vector vaccine (9.3%)	2nd trimester (14.3%), 3rd trimester (85.7%)	Obesity (BMI >30 kg/m ²) (10.7%) smoker (0.7%) alcohol use (0.7%) pregestational diabetes mellitus (4.3%) antenatal medication (32.9%) hypertension on medication (9.3%) twin pregnancy (2.9%)	High-dependency unit admission: was 2% more in vaccinated people than non-vaccinated people, neonatal intensive care unit admission: was 0.3% more in vaccinated people than non-vaccinated people	Fever: was 2.7% more in vaccinated people than non-vaccinated people Postpartum hemorrhage: was 0.8% more in vaccinated people than non-vaccinated people Small for gestational age at birth: were equal Fetal abnormalities: were 0.3% less in vaccinated people than in non-vaccinated people Instrumental delivery: was 5.3% more in vaccinated people than non-vaccinated people	-
18	Peretz-Machluf R (19) Israel	Cohort	3240	PB	N/A	Obesity=BMI ≥30(30.7), Hypertension (1), Diabetes (1)	Gestational diabetes (13.7), preeclampsia (1.2), small for gestational age (12.8), premature pre-labor rupture of membranes (3.1), preterm birth (6), maternal fever (1.7), neonate respiratory complication (1.9), neonate respiratory distress syndrome (0.5), neonate mechanical ventilation (0.8), NICU hospitalization (2.7), neonate hypoglycemia (4.9)	N/A	Significantly decreased percentage of Meconium-stained amniotic fluid in the vaccinated group
19	Toussia-Cohen S (40) Israel	Cohort	162	PB	N/A	Autoimmune disease(19.7)	N/A	Rash/local pain/local swelling (82.7), gastrointestinal symptoms (12.9), fever (9.2), weakness and fatigue (47.5), myalgia (23.4), axillary lymphadenopathy (4.9), remote lymphadenopathy (6.1), paresthesia (4.9), headache (4.9)	N/A
20	Moro PL (41) USA	Cohort	323	PB, M	N/A	N/A	Spontaneous abortion (26), vaginal bleeding (2.5), still birth (1.5), preeclampsia (1.2), preterm delivery (0.6), neonatal death (0.3), birth defects (0.6), NICU admission (0.9)	Headache, fatigue, pyrexia, pain, chills, nausea, pain in extremity, dizziness, injection site pain, vomiting	N/A

NICU: Neonatal Intensive Care Unit; ICU: Intensive Care Unit; SGA: Small for Gestational Age; PB: PfizerBioNTech; M: Moderna; J: Janssen; N/A: not available; ITP: idiopathic thrombocytopenic purpura; BMI: body mass index; CXR: chest X-ray; CPAP: continuous positive airway pressure; TTN: transient tachypnea of the newborn; CT: computed tomography.



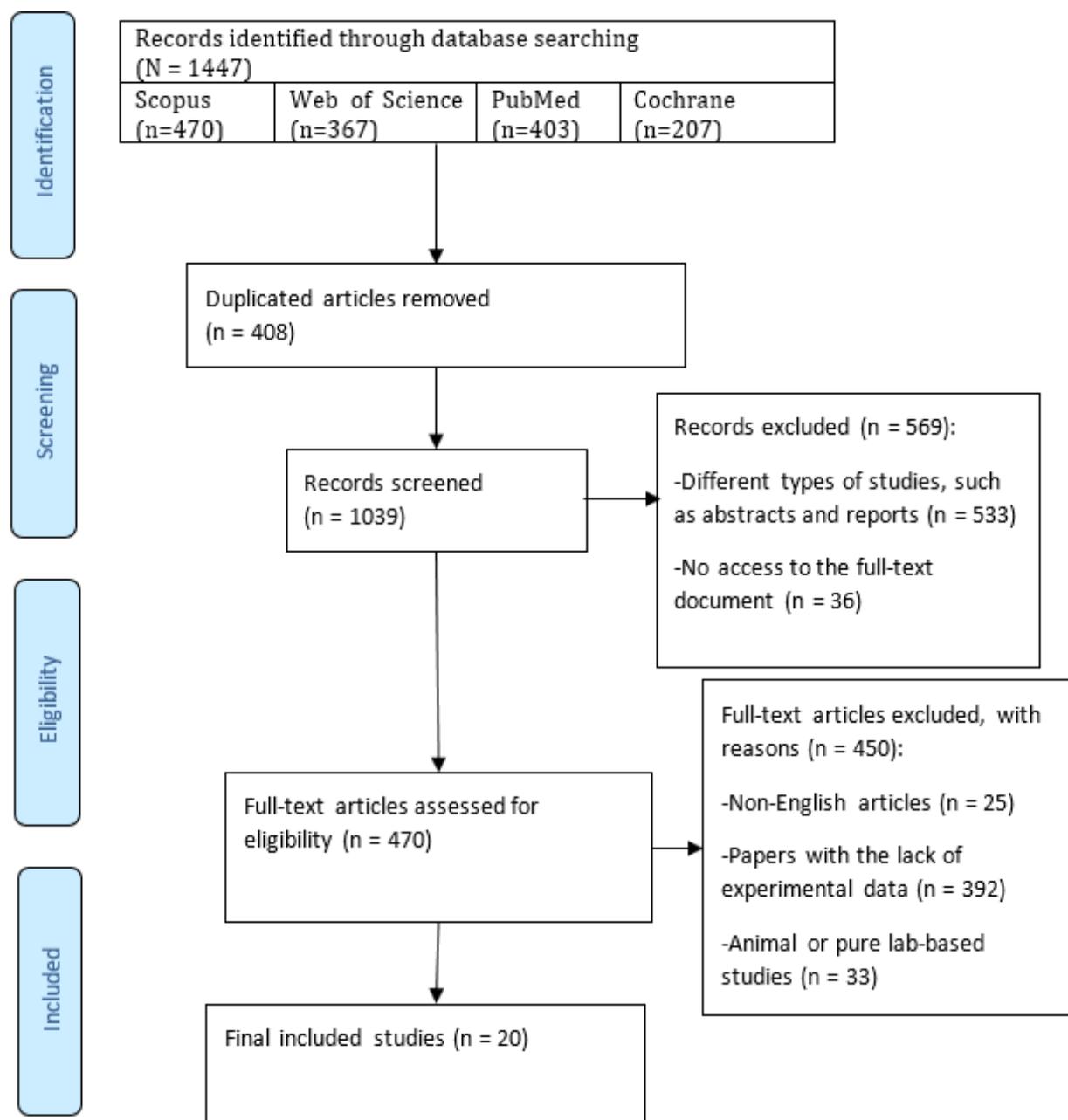


Figure 1: Flow diagram of included studies.

nal bleeding (0.3%) (16). In other included studies, adverse events were as follows: spontaneous abortions, terminated pregnancies, intrauterine growth restriction, anomalies, preterm birth, need for Neonatal Intensive Care Unit (NICU), fetus small for gestational age (24), seizure (25), SARS-CoV-2 hospitalization, abortion, stillbirth, preeclampsia (18), and miscarriages (26).

The main local side effect was injection site pain, and the main systemic side effect was fever. Other local and sys-

temic side effects were as follows: rash, fever, severe fatigue, arthralgia, myalgia, headache, sore arm or pain, fatigue, chills, nausea, vomiting, sweating, feelings of joy, joint pain, swelling, flushing, reduced mental clarity, itching, decreased appetite, decreased sleep quality, palpitations or increased heart rate, heat or cold intolerance, anxiety, heartburn, muscle spasm, nasal congestion, increase in sleep, swollen lymph node and sore throat, dizziness, stomachache, clogged ears, general weakness, non-specified pain, and eye burning or

blurred vision (16-18, 25, 26).

The results of the risk of bias assessment are presented in Table 2. The most common encountered problem was the lack of adequate matching for cases and controls.

4. Discussion

Currently, Pfizer-BioNTech, Moderna, and Janssen vaccines are the main recommended choices for preventing SARS-CoV-2 infection in pregnant women. This review aimed to describe the possible adverse outcome of COVID-19 vaccines among pregnant women using the current evidence. Eight of the included studies were cohort (61.5%), two were cross-sectional, one was case report, and one was case-control. Following Pfizer-BioNTech and Moderna vaccinations, the vast majority of pregnant women reported injection-site pain or soreness (16, 25-27). The most frequently experienced systemic adverse events were fatigue, headache, chills, myalgia, fever, and nausea (16, 25-29). The majority of pregnant women received their vaccine in the second trimester followed by the third trimester and first trimester, respectively (16, 21, 23, 26-28). The adverse events were not statistically different between vaccinated and unvaccinated pregnant women (29). Serious adverse effects that impacted pregnancy, delivery, and neonatal outcomes were reported in some studies (16-18, 20, 21, 25, 27, 29), however; due to lack of information and the absence of a control group, we were not able to infer the causation or comment with certainty about the possible adverse outcomes. Some studies reported no adverse events (22, 23) and found no significant difference between vaccinated and unvaccinated pregnant women (18). Limited data are available on COVID-19 vaccines' efficacy and safety during pregnancy as almost all the vaccine trials excluded this population. Pregnant women and their obstetricians can use available data to weigh the benefits and risks of COVID-19 vaccines, even though they are limited. Most available data come from animal studies and inadvertently exposed pregnant women during vaccine clinical trials and include data concerning the potential risks of vaccines during pregnancy due to vaccine reactogenicity, the timing of vaccination during pregnancy, evidence for the safety of other vaccines during pregnancy, risk of COVID-19 complications in pregnancy among those with underlying conditions, risk of exposure to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and potential for risk mitigation (30). In our study, the majority of pregnant women were vaccinated in the second trimester or median gestational age. Likewise; in Zauche's study, vaccinated pregnant participants were in the second trimester (27). Additionally, in Wainstock's study, women who received the second dose vaccination were at a slightly higher gestational age (29). In the present review, no medical history or underlying disease was

documented in most of the included articles. Likewise, in Trostle's study, the majority of pregnant women had no pre-pregnancy comorbidities (24).

In this review, the main local side effect was injection site pain, and the main systemic side effect was fever. Other local and systemic side effects were rash, fever, severe fatigue, arthralgia, myalgia, headache, sore arm or pain, fatigue, chills, nausea, vomiting, etc. Similarly, in Gray's study, injection site soreness and fever were the most reported side effects (17). In Sukarno's review study, fever, headache, pain, weakness, and arthralgia were common side effects of COVID-19 vaccination in pregnant and lactating women (31). Likewise, Oriji's study showed that the most common side effect was fever and pain at the injection site, but other side effects such as headache, tiredness, and chills were less frequent (32). In another observational study, injection site pain was the most common local side effect in healthcare workers, and fatigue, headache, muscle pain, and chills were the most common systemic side effects; however, fever was less common (33). Fever with non-specific symptoms after COVID-19 vaccination may be due to a common tropical infection, especially if recovery from fever does not occur within 48 hours post-vaccination (34). The reason for the slight variation in the prevalence of complications could be the differences in study population, number of participants, comorbidities, physical conditions, the type of vaccine, and time of vaccination.

Few studies reported serious maternal adverse effects including ITP, axillary adenopathy, vaginal bleeding, uterine contraction and convulsion (16, 25, 35-38). Mild systemic side effects including fever, headache, and fatigue appeared to be similar to non-pregnant women. Hospital admission was reported in one study, but only in 0.2% of cases (18). Most studies have focused on fetus-related complications (16, 21, 23, 24). Major congenital abnormality was rare (22, 23). Pregnancy loss rarely occurred, except in a cohort study from the USA, which reported a relatively high percentage of pregnancy loss, about 13.9%, among 827 pregnant women (23). Premature labor has been mentioned in three studies with an incidence of less than 10% (18, 23, 24). Abortion was reported among 0.7% in one study (26), 1.7% in another study (18) and 2.12% in another one (24); intrauterine growth restriction (IUGR) was reported in 0.5% in one study (18) and 3.2% in another one (23) among pregnant women who received COVID-19 vaccine during their pregnancy. The need for NICU admission was reported only in three studies (16, 21, 26). The reported rates in which were 0.5%, 2.4%, and 15.3%, respectively.



Table 2: Assessment of studies' quality using the Newcastle-Ottawa scale (NOS)

The first author (reference)	Selection (out of 4)	Comparability (out of 2)	Exposure/outcome (out of 3)	Total score (out of 9)
Blakeway, H. (22)	***	**	**	7
Carrie Bennett (20)	***	*	**	6
S. BooksteinPeretz(16)	****	**	*	7
Tom T. Shimabukuro (23)	***	**	***	8
Megan E Trostle(24)	***	**	**	7
Regan N. Theiler (28)	**	**	**	6
Tamar Wainstock(29)	**	*	***	6
Lauren Head Zauche(27)	***	**	***	8
RenukaAnanthKalyanKadali(25)	***	**	**	7
Kathryn J. Gray (17)	***	*	**	6
Collier A-RY (21)	****	**	**	8
Goldstein I (18)	***	*	**	6
Kachikis A (39)	***	**	***	8
Abraham B (35)	***	**	**	7
Ben-Mayor Bashi T (37)	***	*	**	6
Arulappen AL (36)	***	**	**	7
Blakeway H (38)	***	**	***	8
Peretz-Machluf R (19)	****	**	**	8
Toussia-Cohen S (40)	***	**	**	7
Moro PL (41)	***	**	**	7

5. Research implication

Although larger studies and randomized controlled trials (RCTs) are required to address long term and infrequent adverse events and possible side effects associated with COVID-19 vaccination, as well as the effect of vaccination at earlier stages of pregnancy, the current findings support the safety of the mRNA vaccines considering pregnancy and delivery complications. Furthermore, future studies with larger sample sizes, which include vaccine administration in each trimester and evaluation of fetal/neonatal Immunoglobulin transfer via the umbilical cord and breast milk, may help us develop evidence-based recommendations for vaccine administration.

6. Clinical implication

Policy-makers and healthcare professionals (HCPs) should use this knowledge to strongly recommend and advise pregnant women to accept COVID-19 vaccination and encourage them with the extending evidence that the COVID-19 vaccines are safe and effective during pregnancy, considering the maternal morbidity associated with COVID-19 during pregnancy.

7. Limitations

The novelty of the topic and scarcity of research concerning the possible side effects of COVID-19 vaccine in pregnant women limited our ability to provide reliable evidence. Besides, the study design of included studies did not allow for

reliable causal inferences. It is also difficult to clinically randomize pregnant patients into diverse groups for vaccination and therefore, most of the trials excluded this vulnerable population from their study. Thus, it is recommended for future studies to encourage pregnant women to participate to enable the decision-maker to determine the safety of the vaccine.

8. Conclusion

We found that similar to non-pregnant women, pregnant women could experience some local and systemic side effects with no significant difference. Fever and chills, as the systemic side effects, along with local pain and redness, as the local side effects, were the most commonly reported symptoms in pregnant women who received the COVID-19 vaccine. There were also some reports of ITP, adenopathy, vaginal bleeding, uterine contraction and convulsion in some pregnant women. Some studies also reported abortion and premature labor in vaccinated pregnant women. However, these incidences could not certainly be attributed to the COVID-19 vaccine's adverse effects and more longitudinal and experimental studies are needed to define the exact adverse effects of the COVID-19 vaccine in pregnant women.

9. Declarations

9.1. Acknowledgments

The present study was conducted in collaboration with Khalkhal University of Medical Sciences, Iranian Research



Center for HIV/AIDS, Tehran University of Medical Sciences, and Bergen University.

9.2. Authors' contributions

The conception and design of the study: Esmail Mehraeen, SeyedAhmad SeyedAlinaghi

Acquisition of data: Mehrzad MohsseniPour, Solmaz Saeidi
Analysis and interpretation of data: Pedram Habibi, Mohsen Dashti

Drafting the article: Newsha Nazarian, Tayebeh Noori, Zahra Pashaei, AmirBehzad Bagheri, Afsaneh Ghasemzadeh, Amir Masoud

Afsahi, Narjes Aghaie, Paniz Mojdeganlou, Ghazal Arjmand, Ghazal Zargari, Roshanak Modiri, Hengameh Mojdeganlou, Armin Razi

Revising it critically for important intellectual content: SeyedAhmad SeyedAlinaghi, Omid Dadras and Esmail Mehraeen

Final reading and approval of the version to be submitted: all authors

9.3. Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

9.4. Competing interests

The authors declare that there is no conflict of interest regarding the publication of this manuscript.

9.5. Ethics approval and consent to participate

Not applicable

9.6. Consent to publication

Not applicable

9.7. Availability of data and material

The authors stated that all information provided in this article could be share.

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